EXHIBIT A

CHAPTER 58. ANDROGENS - *Peter J. Snyder*

TESTOSTERONE AND OTHER ANDROGENS

Introduction

Synthesis of Testosterone. In men, testosterone is the principal secreted androgen. The Leydig cells synthesize the majority of testosterone by the pathways shown in Figure 58-1. In women, testosterone also is probably the principal androgen and is synthesized both in the corpus luteum and the adrenal cortex by similar pathways. The testosterone precursors androstenedione and dehydroepiandrosterone are weak androgens that can be converted peripherally to testosterone.

Secretion and Transport of Testosterone. The magnitude of testosterone secretion is greater in men than in women at almost all stages of life, a difference that explains almost all other differences between men and women. In the first trimester *in utero,* the fetal testes begin to secrete testosterone, which is the principal factor in male sexual differentiation, probably stimulated by human chorionic gonadotropin (hCG) from the placenta. By the beginning of the second trimester, the value is close to that of midpuberty, about 250 ng/dl (Figure 58-2) (Dawood and Saxena, 1977; Forest, 1975). Testosterone production then falls by the end of the second trimester, but by birth the value is again about 250 ng/dl (Dawood and Saxena, 1977; Forest, 1975), possibly due to stimulation of the fetal Leydig cells by luteinizing hormone (LH) from the fetal pituitary gland. The testosterone value falls again in the first few days after birth, but it rises and peaks again at about 250 ng/dl at 2 to 3 months after birth and falls to <50 ng/dl by 6 months, where it remains until puberty (Forest, 1975). During puberty, from about age 12 to 17 years, the serum testosterone concentration in males increases to a much greater degree than in females, so that by early adulthood the serum testosterone concentration is 500 to 700 ng/dl in men, compared to 30 to 50 ng/dl in women. The magnitude of the testosterone concentration in the male is responsible for the pubertal changes that further differentiate men from women. As men age, their serum testosterone concentrations gradually decrease, which may contribute to other effects of aging in men.

LH, secreted by the pituitary gonadotropes (*see* Chapter 55), is the principal stimulus of testosterone secretion in men, perhaps potentiated by follicle-stimulating hormone (FSH), also secreted by gonadotropes. The secretion of LH by gonadotropes is positively regulated by hypothalamic gonadotropin-releasing hormone (GnRH), while testosterone directly inhibits LH secretion in a negative feedback loop (*see* Chapter 55). LH is secreted in pulses, which occur approximately every 2 hours and are greater in magnitude in the morning. The pulsatility appears to result from pulsatile secretion of GnRH from the hypothalamus. Pulsatile administration of GnRH to men who are hypogonadal due to hypothalamic disease results in normal LH pulses and testosterone secretion, but continuous administration does not (Crowley *et al.*, 1985). Testosterone secretion is likewise pulsatile and diurnal, with the highest plasma concentrations occurring at about 8 A.M. and the lowest at about 8 P.M. The morning peaks diminish as men age (Bremner *et al.*, 1983).

In women, LH stimulates the corpus luteum (formed from the follicle after release of the ovum) to secrete testosterone. Under normal circumstances, however, estradiol and progesterone, not testosterone, are the principal inhibitors of LH secretion in women. Sex hormone-binding globulin (SHBG) binds about 40% of circulating testosterone with high affinity. Because of this high affinity, testosterone bound to SHBG is unavailable for biological effects. Albumin binds almost 60% of circulating testosterone with low affinity, leaving approximately 2% unbound or free. In some testosterone assays, the latter two components are considered as "bioavailable" testosterone.

Metabolism of Testosterone to Active and Inactive Compounds. Testosterone has many different effects in tissues. One of the mechanisms by which the varied effects are mediated is the metabolism of testosterone to two other active steroids, dihydrotestosterone and estradiol (Figure 58-3). Some effects of testosterone appear to be mediated by testosterone itself, some by dihydrotestosterone, and others by estradiol.

The enzyme 5α-reductase catalyzes the conversion of testosterone to dihydrotestosterone. Although

both testosterone and dihydrotestosterone act *via* the androgen receptor, dihydrotestosterone binds with higher affinity (Wilbert *et al.*, 1983) and activates gene expression more efficiently (Deslypere *et al.*, 1992). As a result, testosterone, acting *via* dihydrotestosterone, is able to have effects in tissues that express 5α-reductase that it could not have if it were present only as testosterone. Two forms of 5α-reductase have been identified: type I, which is found predominantly in non-genital skin, liver, and bone, and type II, which is found predominantly in urogenital tissue in men and genital skin in men and women. The effects of dihydrotestosterone in these tissues are described below.

The enzyme complex aromatase (CYP19), which is present in many tissues, especially the liver and adipose tissue, catalyzes the conversion of testosterone to estradiol. This conversion results in approximately 85% of circulating estradiol in men; the remainder is secreted directly by the testes, probably the Leydig cells (MacDonald *et al.*, 1979). The effects of testosterone thought to be mediated *via* estradiol are described below.

Testosterone is metabolized in the liver to androsterone and etiocholanolone (Figure 58-3), which are biologically inactive. Dihydrotestosterone is metabolized to androsterone, androstanedione, and androstanediol.

Physiological and Pharmacological Effects of Androgens

The biological effects of testosterone can be considered by the receptor it activates and by the tissues in which effects occur at various stages of life. Testosterone can act as an androgen either directly, by binding to the androgen receptor, or indirectly by conversion to dihydrotestosterone, which binds to the androgen receptor even more avidly than testosterone. Testosterone also can act as an estrogen by conversion to estradiol, which binds to the estrogen receptor (Figure 58-4).

Effects That Occur Via the Androgen Receptor. Testosterone and dihydrotestosterone act as androgens *via* a single androgen receptor (Figure 58-5). The androgen receptor—officially designated NR3A—is a member of the nuclear receptor superfamily (steroid hormone receptors, thyroid hormone receptors, and orphan receptors). The androgen receptor is comprised of an amino-terminal domain, a DNA-binding domain, and a ligand-binding domain. Testosterone and dihydrotestosterone bind to the ligand-binding domain, causing a conformational change in the receptor that allows the ligand-receptor complex to translocate to the nucleus and bind *via* the DNA-binding domain to androgen response elements on certain responsive genes. The ligand-receptor complex acts as a transcription factor complex and stimulates expression of those genes (Brinkman and Trapman, 2000).

The mechanisms by which androgens have different actions in diverse tissues have become clearer in recent years. One mechanism is the higher affinity with which dihydrotestosterone binds to and activates the androgen receptor compared to testosterone (Deslypere *et al.*, 1992; Wilbert *et al.*, 1983). Another mechanism involves transcription co-factors, both co-activators and co-repressors, which are tissue-specific. At this time, the roles of co-factors are better described for other nuclear receptors than for the androgen receptor (Smith and O'Malley, 2004).

The importance of the androgen receptor is illustrated by the consequences of its mutations. Predictably, mutations that either alter the primary sequence of the protein or cause a single amino-acid substitution in the hormone- or DNA-binding domains result in resistance to the action of testosterone, beginning *in utero* (McPhaul and Griffin, 1999). Male sexual differentiation therefore is incomplete, as is pubertal development.

Another kind of mutation occurs in patients who have spinal and bulbar muscular atrophy, known as Kennedy's disease. These patients have an expansion of the CAG repeat, which codes for glutamine, at the amino terminus of the molecule (Walcott and Merry, 2002). The result is very mild androgen resistance, manifest principally by gynecomastia (Dejager *et al.*, 2002), but progressively severe motor neuron atrophy. The mechanism by which the neuron atrophy occurs is unknown, but similar trinucleotide repeats are associated with a number of other neurological disorders (Masino and Pastore, 2002).

Other kinds of androgen receptor mutations may explain why prostate cancer that is treated by androgen deprivation eventually becomes androgen-independent. Prostate cancer is initially at least partially androgen-sensitive, which is the basis for the initial treatment of metastatic prostate cancer by androgen deprivation. Metastatic prostate cancer often regresses initially in response to this treatment, but then becomes unresponsive to continued deprivation. The androgen receptor not only continues to be expressed in androgen-independent prostate cancer, but its signaling remains active, as indicated by expression of the androgen receptor-dependent prostate-specific antigen. It has been postulated that these observations can be explained by mutations in the androgen receptor gene or changes in androgen receptor co-regulatory proteins (Heinlein and Chang, 2004; Taplin and Balk, 2004).

Effects That Occur Via the Estrogen Receptor. The effects of testosterone on at least one tissue are mediated by its conversion to estradiol, catalyzed by the CYP19 enzyme complex (Figures 58-3 and 58-4). In the rare cases in which a male does not express CYP19 (Carani *et al.*, 1997; Morishma *et al.*, 1995) or the estrogen receptor (Smith *et al.*, 1994), the epiphyses do not fuse and long-bone growth continues indefinitely. In addition, the patients are osteoporotic. Administration of estradiol corrects the bone abnormalities in patients with CYP19 deficiency (Bilizekian *et al.*, 1998), but not in those with an estrogen-receptor defect. Because men have larger bones than women, and bone cells express the androgen receptor (Colvard *et al.*, 1989), testosterone also may have an effect on bone *via* the androgen receptor. Administration of estradiol to a man with CYP19 deficiency increased his libido (Carani *et al.*, 1997), suggesting that the effect of testosterone on male libido may be mediated by conversion to estradiol.

Effects of Androgens at Different Stages of Life. ***In Utero.*** When the fetal testes, stimulated by human chorionic gonadotropin, begin to secrete testosterone at about the eighth week of gestation, the high local concentration of testosterone around the testes stimulates the nearby wolffian ducts to differentiate into the male internal genitalia: the epididymis, vas deferens, and seminal vesicles. Farther away, in the anlage of the external genitalia, testosterone is converted to dihydrotestosterone, which causes the development of the male external genitalia—the penis, scrotum—and the prostate. The increase in testosterone at the end of gestation may result in further phallic growth.

Infancy. The consequences of the increase in testosterone secretion by the testes during the first few months of life are not yet known.

Puberty. Puberty in the male begins at a mean age of 12 years with an increase in the secretion of FSH and LH from the gonadotropes, stimulated by increased secretion of GnRH from the hypothalamus. The increased secretion of FSH and LH stimulates the testes, so, not surprisingly, the first sign of puberty is an increase in testicular size. The increase in testosterone production by Leydig cells, along with the effect of FSH on the Sertoli cells, stimulates the development of the seminiferous tubules, which eventually produce mature sperm. Increased secretion of testosterone into the systemic circulation affects many tissues simultaneously, and the changes in most of them occur gradually during the course of several years. The phallus enlarges in length and width, the scrotum becomes rugated, and the prostate begins secreting the fluid it contributes to the semen. The skin becomes coarser and oilier due to increased sebum production, which contributes to the development of acne. Sexual hair begins to grow, initially pubic and axillary hair, then hair on the lower legs, and finally other body hair and facial hair. Full development of the latter two may not occur until 10 years after the start of puberty and marks the completion of puberty. Muscle mass and strength increase, especially of the shoulder girdle, and subcutaneous fat decreases. Epiphyseal bone growth accelerates, resulting in the pubertal growth spurt, but epiphyseal maturation leads eventually to a slowing and then cessation of growth. Bones also become thicker. The increase in the mass of muscle and bone results in a pronounced increase in body weight. Erythropoiesis increases, resulting in higher hematocrit and hemoglobin concentrations in men than boys or women. The larynx thickens, resulting in a lower voice. Libido develops.

Other changes may result from the increase in testosterone during puberty. Men tend to have a better sense of spatial relations than do women and to exhibit behavior that differs in some ways from that of women, including being more aggressive.

Adulthood. The serum testosterone concentration and the characteristics of the adult male are largely maintained during early adulthood and midlife. One change during this time is the gradual development of male pattern baldness, beginning with recession of hair at the temples and the vertex.

Two changes that can occur in the prostate gland during adulthood are of much greater medical significance. One is the gradual development of benign prostatic hyperplasia, which occurs to a variable degree in almost all men, sometimes obstructing urine outflow by compressing the urethra as it passes through the prostate. This development is mediated by the conversion of testosterone to dihydrotestosterone by 5α-reductase II within prostatic cells (Wilson, 1980).

The other change that can occur in the prostate during adulthood is the development of cancer. Although no direct evidence suggests that testosterone causes the disease, prostate cancer is dependent on testosterone, at least to some degree and at some time in its course. This dependency is the basis of treating metastatic prostate cancer by lowering the serum testosterone concentration (Iversen *et al.*, 1990) or by blocking its action.

Senescence. As men age, the serum testosterone concentration gradually declines (Figure 58-2), and the sex hormone-binding globulin concentration gradually increases, so that by age 80, the total testosterone concentration is approximately 80% and the free testosterone is approximately 40% of that present at age 20 (Harman *et al.*, 2001). This fall in serum testosterone could contribute to several other changes that occur with increasing age in men, including decreases in energy, libido, muscle mass (Forbes, 1976) and strength (Murray *et al.*, 1980), and bone mineral density (Riggs *et al.*, 1982). A causal role is suggested by the occurrence of similar changes seen in men who develop hypogonadism due to disease at a younger age, as discussed below.

Consequences of Androgen Deficiency

The consequences of androgen deficiency depend on the stage of life during which the deficiency first occurs and on the degree of the deficiency.

During Fetal Development. Testosterone deficiency in a male fetus during the first trimester *in utero* causes incomplete sexual differentiation. Testosterone deficiency in the first trimester results only from testicular disease, such as deficiency of CYP17 (17α-hydroxylase); deficiency of LH secretion because of pituitary or hypothalamic disease does not result in testosterone deficiency during the first trimester, presumably because Leydig cell secretion of testosterone at that time is regulated by placental hCG. Complete deficiency of testosterone secretion results in entirely female external genitalia; less severe testosterone deficiency results in incomplete virilization of the external genitalia proportionate to the degree of deficiency. Testosterone deficiency at this stage of development also leads to failure of the wolffian ducts to differentiate into the male internal genitalia, such as the vas deferens and seminal vesicles, but the mullerian ducts do not differentiate into the female internal genitalia as long as testes are present and secrete mullerian inhibitory substance. Similar changes occur if testosterone is secreted normally, but its action is diminished because of an abnormality of the androgen receptor or of 5α-reductase. Abnormalities of the androgen receptor can have quite varied effects. The most severe form results in complete absence of androgen action and a female phenotype; moderately severe forms result in partial virilization of the external genitalia; and the mildest forms permit normal virilization *in utero* and result only in impaired spermatogenesis in adulthood (McPhaul and Griffin, 1999). Abnormal 5α-reductase results in incomplete virilization of the external genitalia *in utero* but normal development of the male internal genitalia, which requires only testosterone (Wilson *et al.*, 1993).

Testosterone deficiency during the third trimester, caused either by a testicular disease or a deficiency of fetal LH secretion, has two known consequences. First, the phallus fails to grow normally. The result, called microphallus, is a common occurrence in boys later discovered to be unable to secrete LH due to abnormalities of GnRH synthesis. Second, the testes fail to descend into the scrotum; this condition, called cryptorchidism, occurs commonly in boys whose LH secretion is subnormal (*see* Chapter 55).

Before Completion of Puberty. When a boy can secrete testosterone normally *in utero* but loses the ability to do so before the anticipated age of puberty, the result is failure to complete puberty. All of the pubertal changes described above, including those of the external genitalia, sexual hair, muscle mass, voice, and behavior, are impaired to a degree proportionate to the abnormality of testosterone secretion. In addition, if growth hormone secretion is normal when testosterone secretion is subnormal during the years of expected puberty, the long bones continue to lengthen because the epiphyses do not close. The result is longer arms and legs relative to the trunk; these proportions are referred to as eunuchoid. Another consequence of subnormal testosterone secretion during the age of expected puberty is enlargement of glandular breast tissue (gynecomastia).

After Completion of Puberty. When testosterone secretion becomes impaired after puberty is completed, regression of the pubertal effects of testosterone depends on both the degree and the duration of testosterone deficiency. When the degree of testosterone deficiency is substantial, libido and energy decrease within a week or two, but other testosterone-dependent characteristics decline more slowly. A clinically detectable decrease in muscle mass in an individual does not occur for several years. A pronounced decrease in hematocrit and hemoglobin will occur within several months. A decrease in bone mineral density probably can be detected by dual-energy x-ray absorptiometry within 2 years, but an increase in fracture incidence would not be likely to occur for many years. A loss of sexual hair takes many years.

In Women. Loss of androgen secretion in women results in a decrease in sexual hair, but not for many years. Androgens may have other important effects in women, and the loss of androgens (especially with the severe loss of ovarian and adrenal androgens that occurs in panhypopituitarism) would result in the loss of these effects. Testosterone preparations that can yield serum testosterone concentrations in the physiological range in women currently are being developed. The availability of such preparations will allow clinical trials to determine if testosterone replacement in androgen-deficient women improves their libido, energy, muscle mass and strength, and bone mineral density.

Therapeutic Androgen Preparations

The need for a creative approach to pharmacotherapy with androgens arises from the fact that ingestion of testosterone is not an effective means of replacing testosterone deficiency. Even though ingested testosterone is readily absorbed into the hepatic circulation, rapid hepatic metabolism ensures that hypogonadal men generally cannot ingest testosterone in sufficient amounts and with sufficient frequency to maintain a normal serum concentration. Therefore most pharmaceutical preparations of androgens are designed to bypass hepatic metabolism of testosterone.

Testosterone Esters. Esterifying a fatty acid to the 17α hydroxyl group of testosterone creates a compound that is even more lipophilic than testosterone itself. When an ester, such as *testosterone enanthate (heptanoate)* (Figure 58-6) or *cypionate (cyclopentylpropionate)* is dissolved in oil and administered intramuscularly every 2 weeks to hypogonadal men, the ester hydrolyzes *in vivo* and results in serum testosterone concentrations that range from higher-than-normal in the first few days after the injection to low-normal just before the next injection (Snyder and Lawrence, 1980) (Figure 58-7). Attempts to decrease the frequency of injections by increasing the amount of each injection result in wider fluctuations and poorer therapeutic outcomes. The undecanoate ester of testosterone (Figure 58-6), when dissolved in oil and ingested orally, is absorbed into the lymphatic circulation, thus bypassing initial hepatic metabolism. *Testosterone undecanoate* in oil also can be injected and produces stable serum testosterone concentrations for a month (Zhang *et al.*, 1998). The undecanoate ester of testosterone is not currently marketed in the United States.

Alkylated Androgens. Adding an alkyl group to the 17α position of testosterone (Figure 58-6) retards hepatic metabolism of the compound. Consequently, 17α-alkylated androgens are androgenic when administered orally; however, they are less androgenic than testosterone itself, and they cause hepatotoxicity (Cabasso, 1994; Petera *et al.*, 1962), whereas native testosterone does not.

Transdermal Delivery Systems. Recent attempts to avoid the first-pass inactivation of

testosterone by the liver have employed novel delivery systems; chemicals called excipients are used to facilitate the absorption of native testosterone across the skin in a controlled fashion. These transdermal preparations provide more stable serum testosterone concentrations than do injections of testosterone esters. The first such preparations were patches, one of which (ANDRODERM) is still available (Dobs *et al.*, 1999). Newer preparations include gels (ANDROGEL, TESTIM) (Marbury *et al.*, 2003; Swerdloff *et al.*, 2000) and a buccal tablet (STRIANT). These preparations produce mean serum testosterone concentrations within the normal range in hypogonadal men (Figure 58-7).

Attempts to Design Selective Androgens

Alkylated Androgens. Decades ago, investigators attempted to synthesize analogs of testosterone that possessed greater anabolic effects than androgenic effects compared to native testosterone. Several compounds appeared to have such differential effects, based on a greater effect on the levator ani muscle compared to the ventral prostate of the rat. These compounds were called anabolic steroids, and most are 17α-alkylated androgens. None of these compounds, however, has been convincingly demonstrated to have such a differential effect in human beings. Nonetheless, they have enjoyed popularity among athletes who seek to enhance their performance, as described below. Another alkylated androgen, 7α-methyl-19-nortestosterone, is poorly converted to dihydrotestosterone (Kumar *et al.*, 1992).

Selective Androgen Receptor Modulators. Stimulated by the development of selective estrogen receptor modulators, which have estrogenic effects in some tissues but not others (*see* Chapter 57), investigators are attempting to develop selective androgen receptor modulators. Indeed, it would be desirable to produce effects of testosterone in some tissues, such as muscle and bone, while avoiding the undesirable effects in other tissues, such as the prostate. Nonsteroidal molecules have been developed that bind to the androgen receptor, and when administered to castrated rats, stimulate the growth of the levator ani more than the prostate (Hanada *et al.*, 2003; Yin *et al.*, 2003). One molecule also improved several properties of bone (Hanada *et al.*, 2003). No human studies have yet been reported.

Therapeutic Uses of Androgens

Male Hypogonadism. The best-established indication for administration of androgens is for the treatment of male hypogonadism (testosterone deficiency in men). Any of the transdermal testosterone preparations or testosterone esters described above can be used to treat testosterone deficiency. Monitoring treatment for beneficial and deleterious effects differs somewhat in adolescents and the elderly from that in other men.

Monitoring for Efficacy. The goal of testosterone therapy for a hypogonadal man is to mimic as closely as possible the normal serum concentration; therefore, serum testosterone concentration must be monitored during treatment. When the serum testosterone concentration is measured depends on the testosterone preparation used. With transdermal patches (*e.g.*, ANDRODERM), the serum testosterone concentration fluctuates during the 24-hour wearing period, with a peak value 6 to 9 hours after application and a nadir (about 50% of the peak) just before the next patch is applied (Dobs *et al.*, 1999). With testosterone gels, the mean serum testosterone concentration is relatively constant from one application to the next (Marbury *et al.*, 2003; Swerdloff *et al.*, 2000). Occasional random fluctuations can occur, however, so measurements should be repeated for any dose. When the enanthate or cypionate esters of testosterone are administered once every 2 weeks, the serum testosterone concentration measured midway between doses should be normal; if not, the dosage schedule should be adjusted accordingly. If testosterone deficiency results from testicular disease, as indicated by an elevated serum LH concentration, adequacy of testosterone treatment also can be judged indirectly by the normalization of LH within 2 months of treatment initiation (Findlay *et al.*, 1989; Snyder and Lawrence, 1980).

Normalization of the serum testosterone concentration induces normal virilization in prepubertal boys and restores virilization in men who became hypogonadal as adults. Within a few months, and often sooner, libido, energy, and hematocrit return to normal. Within 6 months, muscle mass increases and fat mass decreases. Bone density, however, continues to increase for 2 years (Snyder *et al.*,

2000).

Monitoring for Deleterious Effects. When testosterone itself is administered, as in one of the transdermal preparations or as an ester that is hydrolyzed to testosterone, it has no "side effects" (*i.e.,* no effects that endogenously secreted testosterone does not have), as long as the dose is not excessive. Modified testosterone compounds, such as the 17α-alkylated androgens, do have undesirable effects even when dosages are targeted at physiologic replacement. Some of these undesirable effects occur shortly after testosterone administration is initiated, whereas others usually do not occur until administration has been continued for many years. Raising the serum testosterone concentration from prepubertal or midpubertal levels to that of an adult male at any age can result in undesirable effects similar to those that occur during puberty, including acne, gynecomastia, and more aggressive sexual behavior. Physiological amounts of testosterone do not appear to affect serum lipids or apolipoproteins. Replacement of physiological levels of testosterone may occasionally have undesirable effects in the presence of concomitant illnesses. For example, stimulation of erythropoiesis would increase the hematocrit from subnormal to normal in a healthy man, but would raise the hematocrit above normal in a man with a predisposition to erythrocytosis, such as in chronic pulmonary disease. Similarly, the mild degree of sodium and water retention seen with testosterone replacement would have no clinical effect in a healthy man, but would exacerbate pre-existing congestive heart failure. If the testosterone dose is excessive, erythrocytosis, and uncommonly, salt and water retention and peripheral edema occur, even in men who have no predisposition to these conditions. When a man's serum testosterone concentration has been in the normal adult male range for many years, whether from endogenous secretion or exogenous administration, and he is older than 40, he is subject to certain testosterone-dependent diseases, including benign prostatic hyperplasia and prostate cancer.

The principal side effects of the 17α-alkylated androgens are hepatic, including cholestasis, and uncommonly, peliosis hepatis, blood-filled hepatic cysts. Hepatocellular cancer has been reported rarely. Case reports of cancer regression after androgen cessation suggest a possible causal role, but an etiologic link is unproven. The 17α-alkylated androgens, especially in large amounts, may lower serum HDL cholesterol.

Monitoring at the Anticipated Time of Puberty. Administration of testosterone to testosterone-deficient boys at the anticipated time of puberty should be guided by the considerations above, but also by the fact that testosterone accelerates epiphyseal maturation, leading initially to a growth spurt but then to epiphyseal closure and permanent cessation of linear growth. Consequently, the height and growth-hormone status of the boy must be considered. Boys who are short because of growth-hormone deficiency should be treated with growth hormone before their hypogonadism is treated with testosterone.

Male Senescence. Preliminary evidence suggests that increasing the serum testosterone concentration of men whose serum levels are subnormal for no reason other than their age will increase their bone mineral density and lean mass and decrease their fat mass (Amory *et al.*, 2004; Kenny *et al.*, 2001; Snyder *et al.*, 1999a; Snyder *et al.*, 1999b). However, it is entirely uncertain at this time if such treatment will worsen benign prostatic hyperplasia or increase the incidence of clinically detectable prostate cancer.

Female Hypogonadism. It remains to be determined if increasing the serum testosterone concentrations of women whose serum testosterone concentrations are below normal will improve their libido, energy, muscle mass and strength, or bone mineral density.

Enhancement of Athletic Performance. Some athletes take drugs, including androgens, to attempt to improve their performance. Because androgens taken for this purpose usually are taken surreptitiously, information about their possible effects is not as reliable as that for androgens taken for treatment of male hypogonadism.

Kinds of Androgens Used. Virtually all androgens produced for human or veterinary purposes have been taken by athletes. When use by athletes began more than two decades ago, the favored compounds were 17α-alkylated androgens and other compounds that were thought to have greater

anabolic effects than androgen effects relative to testosterone (so-called "anabolic steroids"). Because these compounds can be detected readily by organizations that govern athletic competitions, preparations that increase the serum concentration of testosterone itself, such as the testosterone esters or human chorionic gonadotropin, have increased in popularity. Testosterone precursors, such as androstenedione and dehydroepiandrosterone (DHEA), also have increased in popularity recently because they are considered nutritional supplements and thus are not regulated by national governments or athletic organizations.

A new development in use of androgens by athletes is represented by tetrahydrogestrinone (THG), a potent androgen (Death *et al.*, 2004) that appears to have been designed and synthesized in order to avoid detection by anti-doping laboratories on the basis of its novel structure (Figure 58-6) and rapid metabolism.

Efficacy. There have been few controlled studies of the effects of pharmacological doses of androgens on muscle strength. In one controlled study, 43 normal young men were randomized to one of four groups: strength training with either 600 mg of testosterone enanthate once a week (more than six times the replacement dose) or placebo; or no exercise with either testosterone or placebo. The men who received testosterone experienced an increase in muscle strength compared to those who received placebo, and the men who exercised simultaneously experienced even greater increases (Bhasin *et al.*, 1996). In another study, normal young men were treated with a GnRH analog to reduce endogenous testosterone secretion severely and in a random, blinded fashion, weekly doses of testosterone enanthate from 25 mg to 600 mg. There was a dose-dependent effect of testosterone on muscle strength (Bhasin *et al.*, 2001).

In a double-blind study of androstenedione, men who took 100 mg three times a day for 8 weeks did not experience an increase in muscle strength compared to men who took placebo. Failure of this treatment to increase muscle strength is not surprising, because it also did not increase the mean serum testosterone concentration (King *et al.*, 1999).

Side Effects. All androgens suppress gonadotropin secretion when taken in high doses and thereby suppress endogenous testicular function. This decreases endogenous testosterone and sperm production, resulting in diminished fertility. If administration continues for many years, testicular size may diminish. Testosterone and sperm production usually return to normal within a few months of discontinuation but may take longer. High doses of androgens also cause erythrocytosis (Drinka *et al.*, 1995).

When administered in high doses, androgens that can be converted to estrogens, such as testosterone, cause gynecomastia. Androgens whose A rings have been modified so that they cannot be aromatized, such as dihydrotestosterone, do not cause gynecomastia, even in high doses.

The 17α-alkylated androgens are the only androgens that cause hepatotoxicity. When administered at high doses, these androgens are more likely than others to affect serum lipid concentrations, specifically to decrease high-density lipoprotein (HDL) cholesterol and increase low-density lipoprotein (LDL) cholesterol. Other side effects have been suggested by many anecdotes but have not been confirmed, including psychological disorders and sudden death due to cardiac disease, possibly related to changes in lipids or to coagulation activation.

Certain side effects occur specifically in women and children. Both experience virilization, including facial and body hirsutism, temporal hair recession in a male pattern, and acne. Boys experience phallic enlargement, and women experience clitoral enlargement. Boys and girls whose epiphyses have not yet closed experience premature closure and stunting of linear growth.

Male Contraception. As discussed above, androgens inhibit LH secretion by the pituitary and thereby decrease endogenous testosterone production. Based on these observations, scientists have tried for more than a decade to use androgens—either alone or in combination with other drugs—as a male contraceptive. Because the concentration of testosterone within the testes, approximately one hundred times that in the peripheral circulation, is necessary for spermatogenesis, suppression of endogenous testosterone production greatly diminishes spermatogenesis. Initial use of

testosterone alone, however, required supraphysiologic doses, and addition of GnRH agonists required daily injections. A more promising approach is the combination of a progestin with a physiological dose of testosterone to suppress LH secretion and spermatogenesis, but provide a normal serum testosterone concentration (Bebb *et al.*, 1996). A recent trial employed injections of testosterone undecanoate with a depot progestin every 2 months (Gu *et al.*, 2004). Another androgen being tested as part of a male contraceptive regimen is 7α-methyl-19-nortestosterone, a synthetic androgen that cannot be metabolized to dihydrotestosterone (Cummings *et al.*, 1998).

Catabolic and Wasting States. Testosterone, because of its anabolic effects, has been used in attempts to ameliorate catabolic and muscle-wasting states, but this has not been generally effective. One exception is in the treatment of muscle wasting associated with acquired immunodeficiency syndrome (AIDS), which often is accompanied by hypogonadism. Treatment of men with AIDS-related muscle wasting and subnormal serum testosterone concentrations increases their muscle mass and strength (Bhasin *et al.*, 2000).

Angioedema. Chronic androgen treatment of patients with angioedema effectively prevents attacks. The disease is caused by hereditary impairment of C1-esterase inhibitor or acquired development of antibodies against it (Cicardi *et al.*, 1998). The 17α-alkylated androgens, such as *stanozolol* and *danazol*, stimulate the hepatic synthesis of the esterase inhibitor. In women, virilization is a potential side effect. In children, virilization and premature epiphyseal closure prevent chronic use of androgens for prophylaxis, although they are used occasionally to treat acute episodes.

Blood Dyscrasias. Androgens once were employed to attempt to stimulate erythropoiesis in patients with anemias of various etiologies, but the availability of erythropoietin has supplanted that use. Androgens such as danazol still are used occasionally as adjunctive treatment for hemolytic anemia and idiopathic thrombocytopenic purpura that are refractory to first-line agents.

ANTI-ANDROGENS

Introduction

Because some effects of androgens are undesirable, at least under certain circumstances, agents have been developed specifically to inhibit androgen synthesis or effects. Other drugs, originally developed for different purposes, have been accidentally found to be anti-androgens and now are used intentionally for this indication.

Inhibitors of Testosterone Secretion. Both agonists and antagonists of the GnRH receptor are used to reduce testosterone secretion. Analogs of GnRH effectively inhibit testosterone secretion by inhibiting LH secretion. GnRH "superactive" analogs, given repeatedly, down-regulate the GnRH receptor and are available for treatment of prostate cancer. An extended-release form of the GnRH antagonist *abarelix* (PLENAXIS) is approved for treating prostate cancer (Trachtenberg *et al.*, 2002). Because abarelix does not transiently increase sex steroid production, this preparation may be especially useful in prostate cancer patients in whom any stimulus to tumor growth might have serious adverse consequences, such as patients with spinal cord metastases in whom increased tumor growth could cause paralysis (*see* Chapter 55).

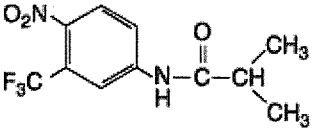
Some antifungal drugs of the imidazole family, such as ketoconazole (*see* Chapter 48), inhibit CYPs and thereby block the synthesis of steroid hormones, including testosterone and cortisol. Because they may induce adrenal insufficiency and are associated with hepatotoxicity, these drugs generally are not used to inhibit androgen synthesis, but sometimes are employed in cases of glucocorticoid excess (*see* Chapter 59).

Inhibitors of Androgen Action

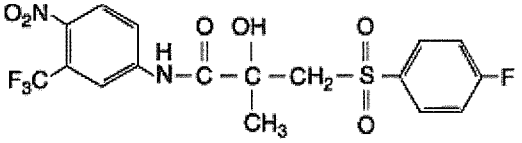
These drugs inhibit the binding of androgens to the androgen receptor or inhibit 5α-reductase.

Androgen Receptor Antagonists. *Flutamide, Bicalutamide, and Nilutamide.* These relatively potent androgen receptor antagonists have limited efficacy when used alone because the increased

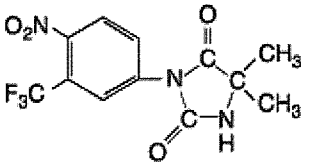
LH secretion stimulates higher serum testosterone concentrations. They are used primarily in conjunction with a GnRH analog in the treatment of metastatic prostate cancer. In this situation, they block the action of adrenal androgens, which are not inhibited by GnRH analogs. Survival rates in groups of patients with metastatic prostate cancer treated with a combination of a GnRH agonist and *flutamide* (EULEXIN), *bicalutamide* (CASODEX), or *nilutamide* (NILANDRON) are similar to one another (Schellhammer *et al.*, 1995) and to survival rates in those treated by castration (Iversen *et al.*, 1990). Bicalutamide is replacing flutamide for this purpose because it appears to have less hepatotoxicity and is taken once a day instead of three times a day. Nilutamide appears to have worse side effects than flutamide and bicalutamide (Dole and Holdsworth, 1997). Flutamide also has been used to treat hirsutism in women, and it appears to be as effective as any other treatment for this purpose (Venturoli *et al.*, 1999). However, the association with hepatotoxicity warrants cautions against its use for this cosmetic purpose.



Flutamide



Bicalutamide



Nilutamide

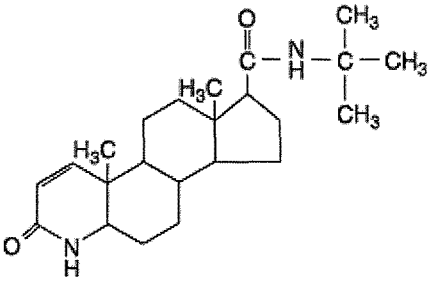
Spironolactone. *Spironolactone* (ALDACTONE) (*see* Chapter 28) is an inhibitor of aldosterone that also is a weak antagonist at the androgen receptor and a weak inhibitor of testosterone synthesis, apparently inhibiting CYP17. When used to treat fluid retention or hypertension in men, gynecomastia is a common side effect (Caminos-Torres *et al.*, 1977). In part because of this adverse effect, the selective mineralocorticoid receptor antagonist *epleronone* (INSPIRA) recently was launched in the United States. Spironolactone is approved by the FDA for treating hirsutism in women, for which it is moderately effective (Cumming *et al.*, 1982); however, it may cause irregular menses.

Cyproterone Acetate. *Cyproterone acetate* is a progestin and a weak anti-androgen by virtue of binding to the androgen receptor. It is moderately effective in reducing hirsutism alone or in combination with an oral contraceptive (Venturoli *et al.*, 1999), but it is not approved for use in the United States.

5α-Reductase Inhibitors. *Finasteride* (PROSCAR) is an antagonist of 5α-reductase, especially type II; *dutasteride* (AVODART) is an antagonist of types I and II; both drugs block the conversion of testosterone to dihydrotestosterone, especially in the male external genitalia. These agents were developed to treat benign prostatic hyperplasia, and they are approved in the United States and many other countries for this purpose. When they are administered to men with moderately severe symptoms due to obstruction of urinary tract outflow, serum and prostatic concentrations of dihydrotestosterone decrease, prostatic volume decreases, and urine flow rate increases (McConnell *et al.*, 1998; Roehrborn *et al.*, 2004; Clark *et al.*, 2004). Impotence is a well-documented, albeit infrequent, side effect of this use, although the mechanism is not understood. Finasteride also is approved for use in the treatment of male pattern baldness under the trade name PROPECIA, even though that effect is presumably mediated *via* type I 5α-reductase. Finasteride appears to be as

effective as flutamide and the combination of estrogen and cyproterone in the treatment of hirsutism (Venturoli *et al.*, 1999).

Finasteride



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